Claim Rejections - 35 USC § 112, first paragraph

Claims 13-22 are rejected under 35 U.S.C. § 112, first paragraph as not being enabled by the specification. Applicant respectfully traverses.

Applicant gratefully confirms the Office Action's acknowledgment of subject matter that is enabled by the specification. This enabled subject matter includes a method of treating ocular cells by administering an adenovirus or adeno-associated virus containing a nucleic acid encoding a protein associated with a genetic ocular disease, where the nucleic acid is expressed so as to alleviate the degeneration of the ocular cells; and a method of treating ocular cells by administering an adenovirus or adeno-associated virus containing a nucleic acid encoding a protein associated with a genetic ocular lysosomal storage disease, where the nucleic acid is expressed so as to alleviate the degeneration of the ocular cells. However, Applicant maintains that the specification enables one skilled in the art to make and use the full scope of the invention as presently.

The present claims are directed to methods of treating a genetic ocular disease by incorporating exogenous nucleic acid into an *in situ* ocular cell under conditions permissive for the uptake of the exogenous nucleic acid, the exogenous nucleic acid encoding a protein associated with the ocular disease, whereby the exogenous nucleic acid is expressed. The present disclosure describes methods that for the first time generated genetically engineered ocular cells *in situ* (*see* claims of priority documents, U.S. Patent Nos. 5,827,702 and 6,204251). The methods provided herein open the door for ocular gene therapy, allowing for treatment of virtually any ocular disease for which a protein associated with the disease or useful for treating the disease is identified.

The Office Action contends that the guidance of the specification and the level of skill in the art do not support the full scope of the claims. In particular, the Office Action contends that full scope of the claims are not supported in regard to: (1) methods of gene delivery into *in situ* ocular cells; (2) vectors for delivering exogenous genes into *in situ* ocular cells; and (3) treating a genetic ocular disease.

Treating a genetic ocular disease

The Office Action states that the specification "fails to provide sufficient guidance demonstrating that any genetic ocular disease ... could be cured or stabilized by the methods of the present invention." (page 5, first paragraph). Applicant respectfully submits that the claimed invention does not require curing or stabilizing a genetic ocular disease.

The claimed invention is directed to methods of treating a genetic ocular disease. The specification, at page 15, lines 6-8, discloses that treatment of an ocular disease means "alleviat[ing] the symptoms of the ocular disease." Applicant's previous response, dated March 7, 2001, exemplified manners in which symptoms could be alleviated by stating that treating can include "curing, stabilizing and slowing the decline of a genetic ocular disease." (page 8, lines 6-7 of previous response).

The claimed method of the invention requires treating a genetic ocular disease, the claimed method does not require curing or stabilizing a genetic ocular disease. One skilled in the art can use the claimed invention to alleviate the symptoms of a genetic ocular disease, which may or may not result in curing or stabilizing the genetic ocular disease. But even if the genetic ocular disease were not cured or stabilized, one skilled in the art would nevertheless

fully be able to carry out the claimed invention if symptoms of the genetic ocular disease were alleviated.

The Office Action appears to contend that if the specification does not enable one skilled in the art to use the claimed invention to cure a genetic ocular disease, the specification would not enable one skilled in the art to alleviate the symptoms of a genetic ocular disease. Applicant respectfully submits that it is not necessary to demonstrate curing a genetic ocular disease in order to demonstrate alleviating symptoms of a genetic ocular disease. Such a requirement would go beyond the plain language of the claims and would set an unreasonable standard which an Applicant must attain in order to simply alleviate symptoms of a disease.

Furthermore, the Office Action has acknowledged that the specification enables a method of treating a degeneration of ocular cells as a result of a genetic ocular disease so as to "alleviate the degeneration" of the ocular cells. Certainly one manner in which the degeneration of ocular cells is alleviated can include curing a genetic ocular disease. Therefore, the Office Action has indicated that a method to alleviate the degeneration of ocular cells is enabled by the specification, but that a method to alleviate the symptoms of a genetic ocular disease is not. Applicant respectfully requests clarification of the standard of enablement used in the Office Action.

Vectors for delivering exogenous genes into *in situ* ocular cells

The Office Action states that although the specification exemplifies expression of β-galactosidase in ocular cells using adenovirus, the "specification fails to provide sufficient guidance demonstrating that a similar gene-transfer in ocular cells could be mediated by any other recombinant viral vectors" (page 8, lines 3-4).

The method of the claimed invention includes incorporating exogenous nucleic acid into an *in situ* ocular cell. The specification teaches a variety of methods for incorporating exogenous nucleic acids into an *in situ* ocular cell. For example, the specification, at page 12, line 25, through page 13, line 1, teaches that exogenous nucleic acids can be incorporated by, for example, retroviral infection, adenoviral infection, transformation with plasmids, transformation with liposomes, bolistic nucleic acid delivery, adeno-associated virus infection and Epstein-Barr virus infection.

In the previous Response, Applicant submitted several references published after the priority date of the present application. The Office Action has indicated that the submitted references demonstrate only adenovirus and adeno-associated virus infection as taught in the specification, and the remaining reference demonstrating HIV infection was not taught in the specification. In order to address this concern of the Office Action, Applicant further provides a variety of additional references published after the priority date of the present application which exemplify more viral and non-viral vectors used to incorporate exogenous nucleic acids into an *in situ* ocular cell.

In Murata et al. (Opthalmic. Res. 29:242-251 (1997), a copy of which is enclosed as Exhibit A), a variety of viral vectors are reviewed for their efficacy in ocular gene therapy. In addition, the reference details introducing a retroviral vector containing the herpes simplex virus thymidine kinase (HSV-TK) into rabbit eyes in order to demonstrate a method for treating proliferative vitreoretinopathy (PVR, see page 249, paragraph bridging left and right columns, and page 250, Figure 3). Specifically, rabbit eyes injected with fibroblasts were prepared as models of PVR (page 246, right column, first paragraph). Expression in ocular cells of retrovirally encoded β-gal and HSV-TK genes was confirmed by *in vitro* studies (page 246, right column, second paragraph through page 249, right column, first paragraph). Next, the

retrovirus encoding HSV-TK was introduced *in situ* into some rabbit eyes while retrovirus that did not encode HSV-TK was introduced *in situ* into control rabbit eyes. Ganciclovir treatment of all rabbits followed the introduction of retroviruses. Rabbit eyes containing the retrovirus encoding HSV-TK demonstrated inhibited PVR development relative to eyes which had received retrovirus that did not encode HSV-TK (page 250, Figure 3). These results, therefore, demonstrate use of a retrovirus to incorporate an exogenous nucleic acid into an *in situ* ocular cell, and expression of the exogenous nucleic acid.

Stetschulte et al. (Invest. Opthamol. Vis. Sci. 42:1975-1975 (2001), a copy of which is enclosed as Exhibit B) teach injection of plasmid DNA (pIRES2-EGFP plasmids encoding the LacZ and $VEGF_{164}$ genes) into the corneal stroma of mice (page 1976, left column, first paragraph and Figure 2). Corneas containing plasmids encoding the LacZ gene demonstrated expression 4 hours after injection (page 1977, Figure 3). Corneas containing plasmids encoding the VEGF gene demonstrated neovascularization and hyphema 7 days after injection (page 1978, Figure 4). Thus, Stetschulte et al. demonstrate use of plasmid DNA to incorporate an exogenous nucleic acid into an *in situ* ocular cell, and expression of the exogenous nucleic acid.

Masuda et al. (Invest. Opthamol. Vis. Sci. 37:1914-1920 (1996), a copy of which is enclosed as Exhibit C) teach introduction of liposomes carrying plasmid DNA into several locations in the eyes of rats (Abstract). Liposomes containing a plasmid encoding the β-gal gene were applied topically to the ocular surface and injected into several portions of the eyes (page 1915, left column, first full paragraph, through page 1916, left column, first full paragraph). Expression of the β-gal gene was observed in a variety of tissues, both when the liposomes were applied topically and when the liposomes were injected (page 1916, Table 1). These results demonstrate use of liposomes

containing exogenous nucleic acid to incorporate the exogenous nucleic acid into an *in situ* ocular cell, and expression of the exogenous nucleic acid.

Tanelian et al. (Biotechniques 23:484-488 (1997), a copy of which is enclosed as Exhibit D) teach a method of incorporating plasmid DNA at a variety of depths into rabbit cornea using bolistic (gene gun) delivery by loading the plasmid onto gold particles (abstract, and page 486, Figure 2). Gold microparticles were coated with plasmid (pUC118) encoding green fluorescent protein (GFP, page 484, right column, second and third full paragraphs). GFP expression in rabbit cornea was visualized *in vivo* and after harvesting the corneas (page 485, first full paragraph). GFP was expressed over the entire 7 days of the experiment (page 486, middle column). Thus, Tanelian et al. demonstrate use of bolistic nucleic acid delivery to incorporate an exogenous nucleic acid into an *in situ* ocular cell, and expression of the exogenous nucleic acid.

In sum, exogenous nucleic acids have been *in situ* incorporated into ocular cells using retroviral infection, plasmid transformation, liposome transformation, and bolistic nucleic acid delivery, as exemplified in Exhibits A, B, C, and D, respectively. Methods such as these are taught in the specification as useful for incorporating exogenous nucleic acid into an *in situ* ocular cell, for example, at page 12, lines 26-31. Accordingly, Applicant maintains that the specification enabled one skilled in the art to use the full scope of methods for incorporating exogenous nucleic acids into an *in situ* ocular cell as recited in the claimed invention.

Methods of gene delivery into *in situ* ocular cells

The Office Action states that the "specification fails to provide sufficient guidance demonstrating that therapeutic effects could be obtained by

all routes of delivering an exogenous nucleic acid encoding a protein associated with an ocular disease" (page 6, lines 6-8). The Office Action points specifically to one method of administering a vector to a subject, *in vivo* vector targeting, contending that the "specification fails to teach a skilled artisan how to overcome the unpredictability for *in vivo* vector targeting such that an efficient transfer and expression of therapeutic transgene to target ocular cells could be achieved by all modes of delivery to achieve the contemplated therapeutic effects." (page 12, lines 5-8). Thus, the Office Action appears to take the position that if there exists one mode of delivering an exogenous nucleic acid which is not taught in the specification, then the specification does not enable one skilled in the art to incorporate an exogenous nucleic acid into an *in situ* ocular cell under conditions permissive for the uptake of the exogenous nucleic acid. Applicant respectfully differs from the opinion of the Office Action.

In the methods of the invention, the methods for treating a genetic ocular disease include incorporating an exogenous nucleic acid into an *in situ* ocular cell under conditions permissive for the uptake of the exogenous nucleic acid. The specification, for example, at page 10, line 32, through page 13, line 3, provides guidance to one skilled in the art of the range of conditions permissive for the uptake of the exogenous nucleic acid. For example, the specification teaches that, "[g]enerally, conditions which allow in vitro uptake of exogeneous cells work for in vivo ocular cells" (page 12, lines 9-11). The specification provides examples in which a solution containing the exogenous nucleic acid is applied directly to the surface of the ocular cells (Example 1, page 20, lines 21-32) or is injected into the eye (Examples 2 and 3, pages 21, line 1 to page 22, line 2). The specification also recites methods for uptake of an exogenous nucleic acid that are known in the art, including bolistic nucleic acid delivery (page 12, line 24 to page 13, line 1). Further, the specification

teaches methods which can be used by one skilled in the art to verify that particular conditions are permissive for the uptake of exogenous nucleic acids (page 12, lines 19-23).

The Office Action contends that, based on the teaching in the specification, one skilled in the art would not be able to use the full scope of the claimed invention because there is one method of delivery, systemic delivery, which is not effective for delivering exogenous nucleic acids to ocular cells. The claimed method of the invention is directed to methods that permit the uptake of an exogenous nucleic acid into an *in situ* ocular cell. The specification teaches conditions which permit the uptake of an exogenous nucleic acid into an *in situ* ocular cell. There is no requirement that the specification teach ***every*** condition that permits the uptake of an exogenous nucleic acid into an *in situ* ocular cell ("even in unpredictable arts, a disclosure of every operable species is not required." MPEP 2164.03). Thus, absence of a teaching of one method of delivery, systemic delivery, for delivering exogenous nucleic acids to ocular cells, is not sufficient to support a prima facie case that the specification does not fully enable the scope of the claims.

In sum, the specification provides one of skill in the art with a variety of methods to incorporate an exogenous nucleic acid into an ocular cell, and with methods for determining conditions permissive for the uptake of the exogenous nucleic acid. Further, the specification is not required to teach every condition that is permissive for the uptake of exogenous nucleic acids into ocular cells. Accordingly, Applicant submits that the specification fully enables the scope of incorporating exogenous nucleic acids into ocular cells as recited in the claimed invention.

Double Patenting

Claims 13-22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims (6, 9-12 and 15-19) of U.S. Patent No. 6,204,251.

Applicant requests that this rejection be held in abeyance until such time as claims are allowed.

Conclusion

Applicant submits that the claims are now in condition for allowance and an early notification of such is solicited.

Respectfully submitted,

FLEHR HOHBACH TEST
ALBRITTON & HERBERT

Date: November 21, 2001

Richard F. Trecartin, Reg. No. 31,801

Four Embarcadero Center, Suite 3400
San Francisco, California 94111
(415) 781-1989